REMARKS

Claims 1-3, 42-45, 89, 90, 102, and 103 are currently pending. New claims 104-121 are supported by the specification and do not contain new matter.[1] The claims stand rejected under 35 U.S.C. 103(a) and 35 U.S.C. 112, first paragraph.

I. 35 U.S.C. 103(a) Rejection

A. The method of claims 1-3, 42, 43, and 90 is not obvious in view of the Reddy et al. and Takahiko et al. references

Reconsideration is requested of the rejection of claims 1-3, 42, 43, and 90 under 35 U.S.C. §103(a) in view of Reddy et al.[2] and Takahiko et al.[3]

Claim 1

Claim 1 is directed toward a method for treating or preventing a neoplasia disorder in a mammal. The method comprises administering to the mammal a therapeutically-effective amount of **celecoxib in combination with gemcitabine**.

Reddy et al. disclose results of a study to assess the ability of celecoxib to suppress the formation of azoxymethane-induced colonic aberrant crypt foci.[4] According to Reddy et al, their results "strengthen the hypothesis that a selective

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[1] Examples 1-9 on pages 143-176 detail the use combination therapy to treat a number of different kinds of neoplasia.

[2] Reddy et al., (1996) Cancer Research 56:4566-4569, of which only the abstract was cited in Paper 11. As such, Applicants' comments detailed above regarding the disclosure of Reddy et al. only reflect review of the abstract.

[3] Takahika et al., (1997) Gan no Rinsho 43(8):836-842, of which only the abstract was cited in Paper 11. As such, Applicants' comments detailed above regarding the disclosure of Takahika et al. only reflect review of the abstract.

[4] Reddy et al., abstract.

COX-2 inhibitor possesses *chemoprotective* activity against colon cancer."[5] But nowhere do Reddy et al. either disclose or suggest the use of celecoxib in combination therapy generally or in combination with gemcitabine for the treatment or prevention of a neoplasia disorder, as required by the method of claim 1.

Takahiko et al. disclose that gemcitabine "inhibits DNA synthesis" and showed "good responses to lung, ovarian, and breast cancer" in phase II trials.[6] Nowhere, however, do Takahiko et al. either disclose or suggest the use of gemcitabine in combination therapy generally or in combination with celecoxib for the treatment or prevention of a neoplasia disorder, as required by the method of claim 1.

The Office asserts that it would have been obvious to combine two compositions, each of which is taught by the prior art to be useful for same purpose, in order to form a third composition that is used for the very same purpose.[7] Reddy et al. and Takahiko et al. provide no basis for this conclusion and do not even disclose any general discussion of combination therapy. There is no motivation, either express or implied, to make the Office's proposed combination. Accordingly, a skilled artisan empowered with the cited art cannot fairly be deemed to be motivated to select celecoxib disclosed in Reddy et al. and combine it with gemcitabine disclosed in Takahiko et al. to form a composition for use in treating a neoplasia disorder, as required by the method of claim 1. As stated in MPEP 2143, where there is no motivation to modify a reference as proposed, the proposed modification is not obvious. The Examiner has effectively slipped into an improper "obvious to try" analysis, informed by hindsight that the Applicants' disclosure affords.

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[5] Reddy et al., abstract.

[6] Takahika et al., abstract.

[7] Paper 11 at page 3.

To support its position, the Office has cited In re Sussman.[8] In Sussman, the inventor claimed a process for the production of unsymmetrical acetals comprising heating an acetal with a dihydric alcohol.[9] The Examiner rejected the inventor's claims in view of either of two patents issued to Carothers (U.S. Patent Nos. 2,071,252 and 2,110,499) stating that the only difference between the process claimed and the prior art was the recital of the product produced.[10] The CCPA affirmed the rejection, holding that the cited art *anticipated* the claimed process because the only difference between the process claimed and the prior art was the recital of the product produced.[11]

The instant situation involving claim 1 and the disclosures of Reddy et al. and Takahiko et al. is distinguishable from Sussman. In Sussman, a single prior art reference contained each element of the claimed invention. The claims, therefore, were found to be **anticipated** in view of the prior art. In the present case, no single reference discloses all of the elements of the claim 1 method. Instead, the claims have been rejected as obvious in view of a combination of two separate references (i.e., Reddy et al. and Takahiko et al.), where the references must be combined in order to arrive at the method of claim 1. But as detailed above, there is **no motivation**, either express or implied, to make the Office's proposed combination. Sussman sheds no light on when two references may properly be combined to support an obviousness rejection and is therefore, not applicable to the present case.

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[8]The Office cited In re Sussman, as 1943 C.D. 518. After an exhaustive search of state and federal case law data bases, Applicants cannot find this case at the cite given by the Office. In their search, the Applicants did find In re Sussman, 141 F.2d 267; 60 U.S.P.Q. 538 (Fed. Cir. 1944), a copy of which is enclosed for the Examiner's convenience. If this is not the case the Examiner is referring to in Paper 11 at page 3, please send a copy of the referenced case to the Applicants for review.

[9]Id. at 538.

[10]Id. at 540.

[11]Id. at 540-541.

For the above reasons, the Office has not established a *prima facie* case that the subject matter of claim 1 would have been obvious to a person of ordinary skill in the art at the time of applicants' invention in view of Reddy et al. and Takahiko et al. Moreover, claims 2-3, 42, 43, 90, and new claims 104, 106, 108, 110, 112, 114, and 116, which depend from claim 1, and likewise non obvious in view of the cited art for the reasons detailed for claim 1 and by way of the additional requirements they introduce.

Claim 118

New claim 118 is directed toward method to *treat* a neoplasia disorder in a mammal, wherein the method comprises administering to the mammal a therapeutically-effective amount of a combination of celecoxib and gemcitabine. As detailed in the specification "treat" is defined as "any process, action, application, therapy, or the like, wherein a mammal, including a human being, is subject to medical aid with the object of improving the mammal's medical condition, directly or indirectly."[12] Per the specification, accordingly, "treat" includes subjects that already have a neoplasia disorder.

Claim 118 is non obvious in view of Reddy et al. and Takahiko et al. Reddy et al., as detailed above, disclose the potential *chemoprotective* effect of celecoxib. Chemoprotective, as disclosed in Reddy et al., includes the use of celecoxib to suppress the formation (i.e, prevent) of azoxymethane-induced colonic aberrant crypt foci. Nowhere does Reddy et al. disclose or suggest that celecoxib is effective to treat colonic aberrant crypt foci or colorectal cancer once it has already developed. A skilled artisan, therefore, would not be motivated to combine the disclosure of Reddy et al. (i.e., use of celecoxib as a chemoprotective agent) with the disclosure of Takahiko et al. (i.e., use of gemcitabine to treat colorectal cancer) to arrive at the method of claim 118, which is directed toward treatment of a neoplasia disorder. Claim 118 is also non obvious in view of the cited art for all the reasons detailed with respect to claim 1.

[12]See page 16 of the specification.

Claim 119

New claim 119 is directed toward a method to *prevent* a neoplasia disorder in a mammal, wherein the method comprises administering to the mammal a therapeutically-effective amount of a combination of celecoxib and gemcitabine.

According to the specification, prevention includes:

> either preventing the onset of clinically evident neoplasia altogether or preventing the onset of a preclinically evident stage of neoplasia in individuals at risk. Also intended to be encompassed by this definition is the prevention of initiation for malignant cells or to arrest or reverse the progression of premalignant cells to malignant cells. This includes prophylactic treatment for those at risk of developing neoplasia.[13]

Claim 119 is non obvious in view of Reddy et al. and Takahiko et al. Reddy et al., as detailed above, disclose the potential *chemoprotective* effect of celecoxib. Takahiko et al. disclose that gemcitabine is effective against "many solid tumors."[14] But nowhere does Takahiko et al. disclose or suggest that gemcitabine is effective for the "prevention" of a neoplasia disorder. A skilled artisan, therefore, would not be motivated to combine the disclosure of Reddy et al. (i.e., use of celecoxib as a chemoprotective agent) with the disclosure of Takahiko et al. (i.e., use of gemcitabine to treat colorectal cancer) to arrive at the method of claim 119, which is directed toward **prevention** of a neoplasia disorder. Claim 119 is also non obvious in view of the cited art for all the reasons detailed with respect to claim 1.

B. The method of claims 44, 45, 89, 102 and 103 is not obvious in view of the Reddy et al., Takahiko et al. and Aleman et al. references

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[13]See pages 16-17 of the specification.

[14]Takahika et al., abstract.

Reconsideration is requested of the rejection of claims 44, 45, 89, 102 and 103 under 35 U.S.C. §103(a) in view of Reddy et al., Takahiko et al., and in further view of Aleman et al.[15]

Claim 44 is directed toward a method for treating or preventing a neoplasia disorder in a mammal. The method comprises administering to the mammal a therapeutically-effective amount of **celecoxib** and **gemcitabine in combination with radiation therapy**.

The disclosure of Reddy et al. and Takahiko et al. is detailed in IA. above. Neither reference, taken singly or combined, render claim 44 obvious. Reddy et al. do not disclose or suggest a combination that includes either radiation therapy or gemcitabine for use in the treatment of a neoplasia disorder. Similarly, Takahiko et al. do not disclose or suggest a combination that includes either radiation therapy or celecoxib for use in the treatment of a neoplasia disorder.

According to the disclosure of Aleman et al., radiotherapy "has become an integral part of the multi disciplinary approach in the treatment of colorectal cancer."[16] Aleman et al. further disclose that radiotherapy is sometimes administered in "combination with chemotherapy," or in "a pre or postoperative setting."[17] But Aleman et al. do not disclose or suggest which of many available chemotherapeutic agents to select for use in combination therapy and fail to disclose or suggest the use of either celecoxib or gemcitabine. None of Reddy et al., Takahiko et al., or Aleman et al. offer any guidance that would have enabled one skilled in the art to select celecoxib, gemcitabine and radiation therapy to prepare the combination of claim 44.

According to the Office, it would have been obvious to combine two compositions with radiation therapy, each of which is taught by the prior art to be useful for same purpose, in order to form a therapy that is used for the very

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[15]Aleman et al., (1995) European Journal of Cancer 31A(7/8) 1333-1339, of which only the abstract was cited in Paper 11. As such, Applicants' comments detailed above regarding the disclosure of Aleman et al. only reflect review of the abstract.

[16]Aleman et al., abstract.

[17]Aleman et al., abstract.

same purpose.[18] Reddy et al., Takahiko et al. and Aleman et al. provide no basis for this conclusion and do not even disclose any general discussion of combination therapy. As stated in MPEP 2143, where there is no motivation to modify a reference as proposed, the proposed modification is not obvious.

The Office has effectively slipped into an improper "obvious to try" analysis, informed by hindsight that Applicants' disclosure affords. But the courts have consistently held that the test for a *prima facie* case of obviousness is not whether an invention is obvious to try.[19] Instead, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references, and there must be some reasonable expectation of success. The Office has not met this legal standard. The Office has provided no reason or rationale as to why a skilled artisan would be motivated to combine the disclosure of three separate references, Reddy et al., Takahiko et al., and Aleman et al., to arrive at the method of claim 44. For example, why would it have been obvious to combine a reference that has general disclosure about the potential use of celecoxib for the prevention of cancer with yet another reference that has general disclosure about the potential use of gemcitabine for the treatment of cancer and still combine both of those disclosures with yet another disclosure about radiation-when not one of the references even mentions any of these other agents or combination therapy in general? Instead, the Office asserts in 8 lines of bare assertions what each reference purportedly discloses and then simply concludes that claim 44 is obvious. To properly establish a *prima facie* case of obviousness, as noted above, the law requires more than conclusions supported by bare assertions.

For the foregoing reasons, the Office has failed to establish that claim 44 is *prima facie* obvious in view of Reddy et al., Takahiko et al., and Aleman et al. Moreover, claims 45, 89, 102, 103, and new claims 105, 107, 109, 111, 113, and 117, which depend from claim 44, are likewise patentable over these references

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[18]Paper 11 at page 3.

[19] See In re O'Farrell, 7 U.S.P.Q.2d 1673, 1680-81 (Fed. Cir. 1988).

for the reasons stated with respect to claim 44 and by reason of the additional requirements they introduce.

Claim 120

New claim 120 is directed toward a method to *treat* a neoplasia disorder in a mammal, wherein the method comprises administering to the mammal a therapeutically-effective amount of a combination of radiation therapy, celecoxib and gemcitabine. As detailed in the specification "treat" is defined as "any process, action, application, therapy, or the like, wherein a mammal, including a human being, is subject to medical aid with the object of improving the mammal's medical condition, directly or indirectly."[20] Per the specification, accordingly, "treat" includes subjects that already have a neoplasia disorder.

Claim 120 is non obvious in view of Reddy et al., Takahiko et al. and Aleman et al. Reddy et al., as detailed above, disclose the potential *chemoprotective* effect of celecoxib. Chemoprotective, as disclosed in Reddy et al., includes the use of celecoxib to suppress the formation (i.e, prevent) of azoxymethane-induced colonic aberrant crypt foci. Nowhere does Reddy et al. disclose or suggest that celecoxib is effective to **treat** colonic aberrant crypt foci or colorectal cancer once it has already developed. Takahiko et al. disclose that gemcitabine is effective against "many solid tumors"[21] and Aleman et al. disclose that radiation is used for "the *treatment* of colorectal cancer."[22] A skilled artisan, therefore, would not be motivated to combine the disclosure of Reddy et al. (i.e., use of celecoxib as a chemoprotective agent) with the disclosure of Takahiko et al. (i.e., use of gemcitabine to treat colorectal cancer) and with the disclosure of Aleman et al. (i.e. use of radiation to treat cancer) to arrive at the method of claim 120, which is directed toward **treatment** of a neoplasia disorder. Claim 120 is also non obvious in view of the cited art for all the reasons detailed with respect to claim 1.

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[20]See page 16 of the specification.

[21]Takahika et al., abstract.

[22]Aleman et al., abstract.

Claim 121

New claim 121 is directed toward a method to *prevent* a neoplasia disorder in a mammal, wherein the method comprises administering to the mammal a therapeutically-effective amount of a combination of radiation therapy, celecoxib and gemcitabine. According to the specification, prevention includes:

> either preventing the onset of clinically evident neoplasia altogether or preventing the onset of a preclinically evident stage of neoplasia in individuals at risk. Also intended to be encompassed by this definition is the prevention of initiation for malignant cells or to arrest or reverse the progression of premalignant cells to malignant cells. This includes prophylactic treatment for those at risk of developing neoplasia.[23]

Claim 121 is non obvious in view of Reddy et al., Takahiko et al. and Aleman et al. Reddy et al., as detailed above, disclose the potential *chemoprotective* effect of celecoxib. Chemoprotective, as disclosed in Reddy et al., includes the use of celecoxib to suppress the formation (i.e, prevent) of azoxymethane-induced colonic aberrant crypt foci. Takahiko et al. disclose that gemcitabine is effective against "many solid tumors"[24] and Aleman et al. disclose that radiation is used for "the *treatment* of colorectal cancer."[25] But nowhere do either Takahiko et al. or Aleman et al. disclose or suggest that gemcitabine or radiation are effective for the "prevention" of a neoplasia disorder. A skilled artisan, therefore, would not be motivated to combine the disclosure of Reddy et al. (i.e., use of celecoxib as a chemoprotective agent) with the disclosure of Takahiko et al. (i.e., use of gemcitabine to treat colorectal cancer) and further with the disclosure of Aleman et al. (i.e, use of radiation to treat cancer) to arrive at the method of claim 121, which is directed toward **prevention** of a neoplasia

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[23]See pages 16-17 of the specification.

[24]Takahika et al., abstract.

[25]Aleman et al., abstract.

disorder. Claim 121 is also non obvious in view of the cited art for all the reasons detailed with respect to claim 1.

II. 35 U.S.C. 112, First Paragraph Rejection

Reconsideration is requested of the rejection of claims 1-3, 44, 102, and 103 under 35 U.S.C. 112, first paragraph. The Office has asserted that these claims are not sufficiently enabled by the specification.

The standard for enablement is whether one of ordinary skill in the art could make or use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation.[26] In this case, the specification coupled with information generally known in the art, fully enables a person of ordinary skill to identify and prepare a composition comprising celecoxib and gemcitabine for use in the method of claim 1 or a composition comprising celecoxib and gemcitabine in combination with radiation therapy for use in the method of claim 44 **without undue experimentation**. The specification discloses the chemical structure of celecoxib, how to make it, and how to administer it in combination therapy for the treatment of neoplasia.[27] In addition, the specification discloses the chemical structure of gemcitabine, how to make it, and how to administer it in combination therapy for the treatment of neoplasia.[28] Moreover, the specification provides detailed instruction regarding the type of radiation, its administration, and its use in combination

[26]U.S. v. Teletronics, Inc., 8 USPQ2d 1217 (Fed. Cir. 1988).

[27]For the chemical formula of celcoxib, see page 42 of the specification. Description of how to make celecoxib is detailed on page 42 of the specification and in more detail in U.S. Patent No. 5,466,823. Examples 1-9 on pages 143-176 detail the use of celecoxib in combination therapy to treat a number of different kinds of neoplasia.

[28]For the chemical structure of gemcitabine and a description of how to make it, see page 72 of the specification (and U.S. Patent No. 4,526,988). Examples 1-9 on pages 143-176 detail the use of celecoxib in combination therapy to treat a number of different kinds of neoplasia.

therapy.[29] The specification also details over 85 examples[30] of neoplasia disorders that may be treated by the method of claim 1 or claim 44 and also contains nine examples[31] that illustrate the use of combination therapy to treat lung cancer, colorectal cancer, breast cancer, prostate cancer, bladder cancer, pancreas cancer, ovary cancer, and central nervous system cancer. In view of this disclosure, a skilled artisan is sufficiently empowered to make and use the method of claim 1 or 44 without undue experimentation.

According to the Office, however, the specification is enabling for the specific neoplasia disorders disclosed,[32] but not for neoplasia disorders not specifically identified in the specification. The Office asserts that "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to use the invention *commensurate in scope* with these claims."[33] In arriving at this conclusion, the Office relied on In re Wands.[34] In the Wands case, the claim at issue required using an antibody "wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least $10^9 M^{-1}$."[35] The Federal Circuit discussed several of the relevant factors, and concluded that "undue experimentation would not be required to practice the invention."[36] Contrary to the Office's assertion, however, Wands supports the conclusion that claims 1 and 44 are sufficiently enabled.

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[29]See page 20 and Examples 1-9 on pages 143-176 detail the use of radiation in combination therapy to treat a number of different kinds of neoplasia.

[30]See pages 10-11 of the specification.

[31]Examples 1-9 on pages 143-176 detail the use of celecoxib in combination therapy to treat a number of different kinds of neoplasia.

[32]Paper 11 at page 4.

[33]Paper 11 at page 4.

[34]In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

[35]*Id.*, at 8 USPQ2d p. 1402.

[36]*Id.*, at 8 USPQ2d p. 1406.

One factor considered in Wands was the "breadth of the claims." The Federal Circuit noted that of 143 candidate antibodies produced by Wands, his testing of just nine and proving the required activity of just four, not even considering countless others which Wands did not make, was sufficient to support claims of the following breadth: "wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9M^{-1}."[37] This breadth, deemed acceptable, is much broader than a claim limited to those antibodies that Wands either produced or tested. Against this background, the breadth of claim 1 and 44, in terms of the use of "neoplasia disorder," is reasonable in light of the 85 examples of specific types of neoplasia disorders identified in the specification and nine examples[38] that illustrate the use of combination therapy to treat lung cancer, colorectal cancer, breast cancer, prostate cancer, bladder cancer, pancreas cancer, ovary cancer, and central nervous system cancer. Patent applicants are not required to show a specific example for every possible embodiment of the claimed invention, so long as the specification and the general knowledge of the art would enable one of ordinary skill in the art to make and use the invention.[39]

For the foregoing reasons, the Office has failed to establish that claim 1 and 44 are not sufficiently enabled. Moreover, claims 2-3 and 102-103 are likewise enabled for all of the reasons detailed regarding claim 1 and 44.

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[37] In re Wands, at 8 USPQ2d 1405.

[38] Examples 1-9 on pages 143-176 detail the use of celecoxib in combination therapy to treat a number of different kinds of neoplasia.

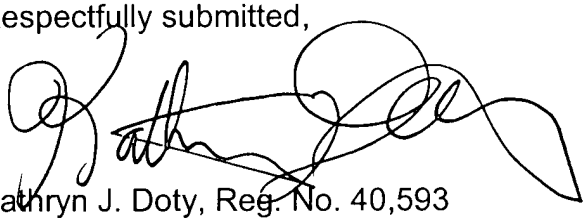
[39] In re Borkowski, 164 U.S.P.Q. 642, 645 (CCPA 1970).

III. Conclusion

In light of the foregoing, Applicants request entry of the claim amendments, withdrawal of the claim rejections, and solicit an allowance of the claims. The Examiner is invited to contact the undersigned attorney should any issues remain unresolved.

A check in the amount of $ 344.00 is enclosed in payment of the fee for added independent claims. The Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,



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